LAW OFFICES
KELLER AND HECKMAN LLP
1001 G STREET, N.W.
SUITE 500 WEST
WASHINGTON, D.C. 20001
TELEPHONE (202) 434-4100
FACSIMILE (202) 434-4646

25 RUE BLANCHE
B-1060 BRUSSELS
TELEPHONE 32(2) 541 05 70
FACSIMILE 32(2) 541 05 80

WWW.KHLAW.COM

JOSEPH E. KELLER (1907-1994)
JEROME H. HECKMAN
WILLIAM H. BORGHESANI, JR
MALCOLM D. MACARTHUR
WAYNE V. BLACK
TERRENCE D. JONES
MARTIN W. BERCOVICI
JOHN S. ELDRED
RICHARD J. LEIGHTON
ALFRED S. REGNERY
DOUGLAS J. BEHR
RAYMOND A. KOWALSKI*
MICHAEL F. MORRONE
JOHN B. RICHARDS
JEAN SAVIGNY*◊
JOHN B. SUBECK
PETER L. DE LA CRUZ
MELVIN S. DROZEN
LAWRENCE P. HALPRIN
RALPH A. SIMMONS
RICHARD F. MANN

C. DOUGLAS JARRETT
SHEILA A. MILLAR
GEORGE G. MISKO
PATRICK J. HURD
DAVID G. SARVADI
CATHERINE R. NIELSEN
MARK MANSOUR*
ELLIOT BELILOS
JEAN-PHILIPPE MONTFORT*◊
JOAN C. SYLVAIN◊
JUSTIN C. POWELL
GEORGE BRENT MICKUM, IV
COLETTE FERRIS-SHOTTON
ARTHUR S. GARRETT III
ROBBIE S. PITT
ELIZABETH N. HARRISON
JOHN B. RODGERS
MARTHA E. MARRAPESE
PETER A. SAARI*
NEGIN MOHTADI
NICOLE B. DONATH
DAVID R. JOY
FREDERICK A. STEARNS

TODD A. HARRISON*
JOHN F. FOLEY
TONYE RUSSELL EPPS
THOMAS C. BERGER
RACHIDA SEMAIL*◊
JOHN DOBINSON*◊
DANIEL QUINTART*◊
KOMAL J. HERSHBERG
PAULA DEZA
JOHN B. O'LOUGHLIN, JR.
DEVON WM. HILL
N. AJOY MATHEW
JOANNA R. SOFFA
AMY E. FORTENBERRY
PAMELA L. GAUTHIER
COLLEEN M. EVALE
ANN M. BOECKMAN*
SANA D. COLEMAN
DEBORAH W. ZIFFER*
JEFFREY A. KEITHLINE*
MICHAEL D. OLSEN*
MICHELLE L. DAUPHINAIS*
FRANK J. VITOLO*

*NOT ADMITTED IN D.C.
◊RESIDENT BRUSSELS

SCIENTIFIC STAFF

DANIEL S. DIXLER, PH. D.
CHARLES V. BREDER, PH. D.
ROBERT A. MATHEWS, PH. D., D.A.B.T.
JOHN P. MODDERMAN, PH. D.
(1944-1998)
HOLLY HUTMIRE FOLEY
JANETTE HOUK, PH. D.
LESTER BORODINSKY, PH. D.
THOMAS C. BROWN
MICHAEL T. FLOOD, PH. D.
ANNA GERGELY, PH. D.◊
STEFANIE M. CORBITT
JUSTIN J. FREDERICO, PH. D.
ROBERT J. SCHEUPLEIN, PH. D.
RACHEL F. JOYNER
ELIZABETH A. HEGER

TELECOMMUNICATIONS
ENGINEER
RANDALL D. YOUNG

September 14, 1999

WRITER'S DIRECT ACCESS
(202) 434-4110
heckman@khlaw.com

Hand Delivered

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Number 99N-0193; Proposed Rule to Amend 21 C.F.R. § 314.70 on Supplements and Other Changes to an Approved Application

On behalf of the Food, Drug, and Cosmetic Packaging Materials Committee of The Society of the Plastics Industry, Inc. (SPI), we hereby respectfully submit these comments on the above-referenced Proposal to amend 21 C.F.R. § 314.70, "Supplements and changes to an approved application" (64 *Fed. Reg.* 34608 (June 28, 1999)).[1/] Our comments focus on the heightened reporting requirements applicable to changes within packaging materials for sterile liquid dosage forms.

Section 314.70 currently provides for three separate reporting categories for changes to an approved new drug application: (1) changes that must be reported in a supplemental new drug application (SNDA) and approved before the change is made; (2) changes that must be reported in an SNDA, but which may be made before Agency approval; and (3) changes that do not require

---

1/ The Society of the Plastics Industry, Inc is the trade association representing the fourth-largest manufacturing industry in the United States. SPI's 2,000 members represent the entire plastics industry supply chain, including processors, machinery and equipment manufacturers and raw material suppliers. The U.S. plastics industry employs 1.3 million workers and provides $274 billion in annual shipments. Founded in 1937, SPI is the voice of the plastics industry. The Food, Drug, and Cosmetic Packaging Materials Committee is composed of representatives of SPI member companies with special interest and expertise in packaging materials for drugs and other FDA-regulated products

99N-0193

C 29

Food and Drug Administration (FDA) approval and that may simply be reported in the applicant's annual report. The Proposed Rule would amend Section 314.70 to provide for four reporting categories for changes: (1) changes that must be reported in a supplement requiring FDA prior approval ("major changes"); (2) changes that require a supplement submission at least 30 days prior to distribution of the drug product made with the change ("moderate changes"); (3) changes that may be implemented when the Agency receives a supplement (also considered "moderate changes"); and (4) changes that may be described in the next annual report ("minor changes").

The Proposed Rule, without further explanation, alters the reporting category applicable to changes within the container/closure system for sterile liquid drugs that are made based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (for example, the United States Pharmacopeia (USP)). Under paragraph (d)(6) of the current regulation, these changes are described in the annual report and do not require FDA prior approval.[2/] Paragraphs (c)(2)(i) and (d)(2)(v) of the Proposed Rule, as further explained in the agency's draft guidance document entitled, "Guidance for Industry: Changes to an Approved NDA or ANDA," would require a supplement to be filed for any change within the container/closure system for a sterile liquid dosage form. This filing requirement would apply even if the change is made based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

The Agency has not provided any rationale for its proposal to require a supplement to be filed in connection with any change within a packaging material for a sterile liquid drug even in situations in which the change is based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium. This requirement, in effect, would mandate duplicative FDA review of equivalency protocols in some cases, and would undermine the utility of USP monographs in others.

In cases in which an equivalency protocol is provided in a new drug application, that protocol is reviewed by the Agency in connection with the application. The Agency has the ability to review the protocol at that time to determine whether it is sufficient to demonstrate equivalency for packaging the types of drugs covered by the application, including sterile liquid dosage forms if they are the subject of the application. Once the application is approved, the applicant considers that an equivalency protocol in the application has been shown, to FDA's satisfaction, to demonstrate the equivalency of a packaging material. It is unduly burdensome to subject a change made based on that protocol to an additional FDA review and approval prior to implementation.

2/ Under paragraph (b)(2)(vii) of the current regulation, a change in the type of container and closure material for a drug product (for example, from glass to high density polyethylene (HDPE) or from HDPE to polyvinyl chloride) require the submission of an SNDA and FDA prior approval.

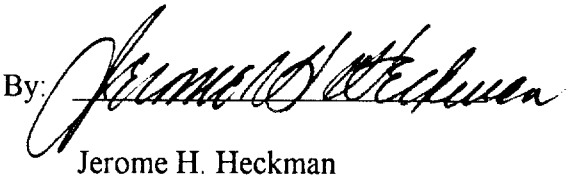
In the same way, it would be unduly burdensome to require FDA prior approval for a change within a container/closure system for a material based on a determination of equivalency made in accordance with a USP monograph that is specifically designed for that purpose. For example, the USP monograph for "Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles" provides standards and tests to characterize PET and PETG bottles "that are interchangeably suitable for packaging liquid oral dosage forms." (*See* United States Pharmacopeia 24 Part <661> p. 1934 (2000 ed.).) FDA is provided with the opportunity to review and comment on USP monographs before they are published in final form; thus, the requirement for an additional Agency prior review of a change made in accordance with a USP monograph is unnecessary.

Consequently, we respectfully request that FDA amend the language of paragraphs (c)(2)(i) and (d)(2)(v) of the Proposed Rule to continue to permit companies to make changes within packaging materials for all types of drugs, including sterile liquid drugs, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

SPI appreciates the opportunity to comment on FDA's Proposed Rule to amend Section 314.70. The Society would be pleased to respond to requests from the Agency for additional information pertaining to these comments.

Respectfully submitted,

THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

By: 

Jerome H. Heckman
GENERAL COUNSEL